Regulation of IGF1R mRNA expression by GnRH agonist may be involved in decreasing height velocity during Central Precocious Puberty treatment.

Mariana T A Sarti de Paula[1], Rafaela Ricco[1], Rodrigo J. Custodio[1], Soraya S. Milani[1], Patrícia V.S. Atique[1], Ayrton C. Moreira[2], Sonir R.R. Antonini[1], Raphael Del Roio Liberatore Jr[1], Carlos E. Martinelli Jr[1].
Departments of Paediatrics[1] and Medicine[2], Ribeirão Preto Medical School-USP, Ribeirão Preto, Brazil.

DEPARTMEN OF PAEDIATRICS FMRP- USP

BACKGROUND: Growth spurt is a major event in central precocious puberty (CPP). GnRH analogue (GnRHa) treatment inhibit gonadal axis and decrease height velocity. However, serum IGF-I and IGFBP-3 remain high as before treatment. No reports regarding IGF type 1 receptor (IGF1R) in CPP is available.

AIM: to study IGF1R mRNA expression in girls with CPP before and during GnRHa treatment.

MÉTHODS: 34 girls with CPP were studied. 16 were evaluated before treatment (Group A) and 17 in use of GnRHa (Group B). 18 Age-matched pre pubertal children we studied as controls. Fasting blood sample were collect for IGF1R mRNA expression analysis in peripheral lymphocytes (RT-PCR) and serum IGF-I, IGFBP-3 (IMMULITE 2000), IGFBP-1 (ELISA) and insulin (IRMA) determination. IGF-I was also adjusted for age and sex : (Patient value-P50)/P50.
Statistical Analysis: Kruskal-Wallis, Mann Whitney and Wilcoxon tests were used in the analysis. P<0.05 was assumed as significant.
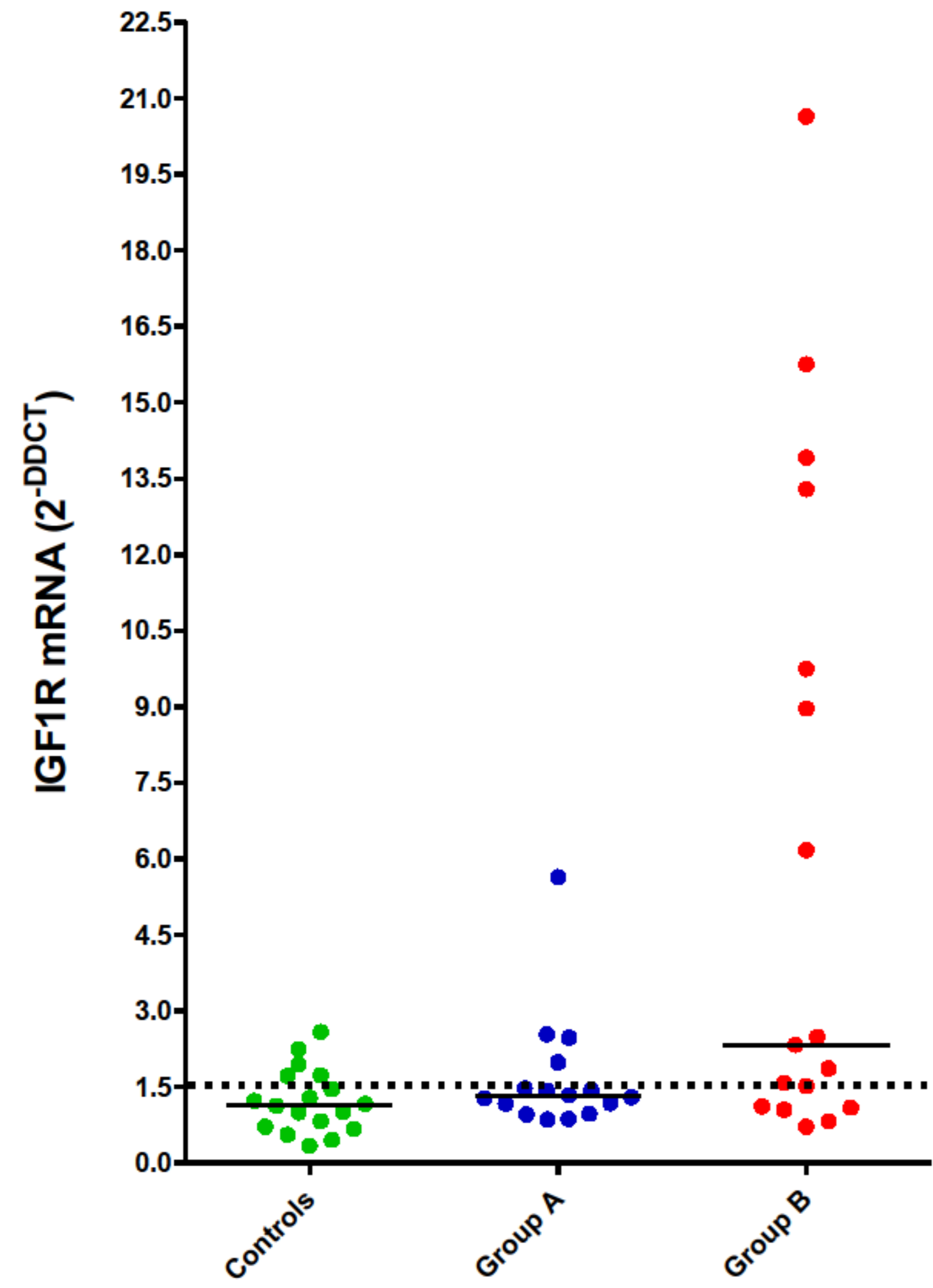
RESULTS

Figure 1: Expression of IGF1R mRNA ($2^{-\Delta\Delta CT}$) in controls, Group A and Group B. Bars represent medians.

The expression of IGF1R mRNA was higher in Group B than in Group A (p=0.03) and Controls (p=0.03). No difference was observed between Groups A and Controls.

Considering 1.5 as cut-off value (controls mean + 2SE), high expression of IGF1R mRNA was more frequent in Group B than in Group A (p=0.01).
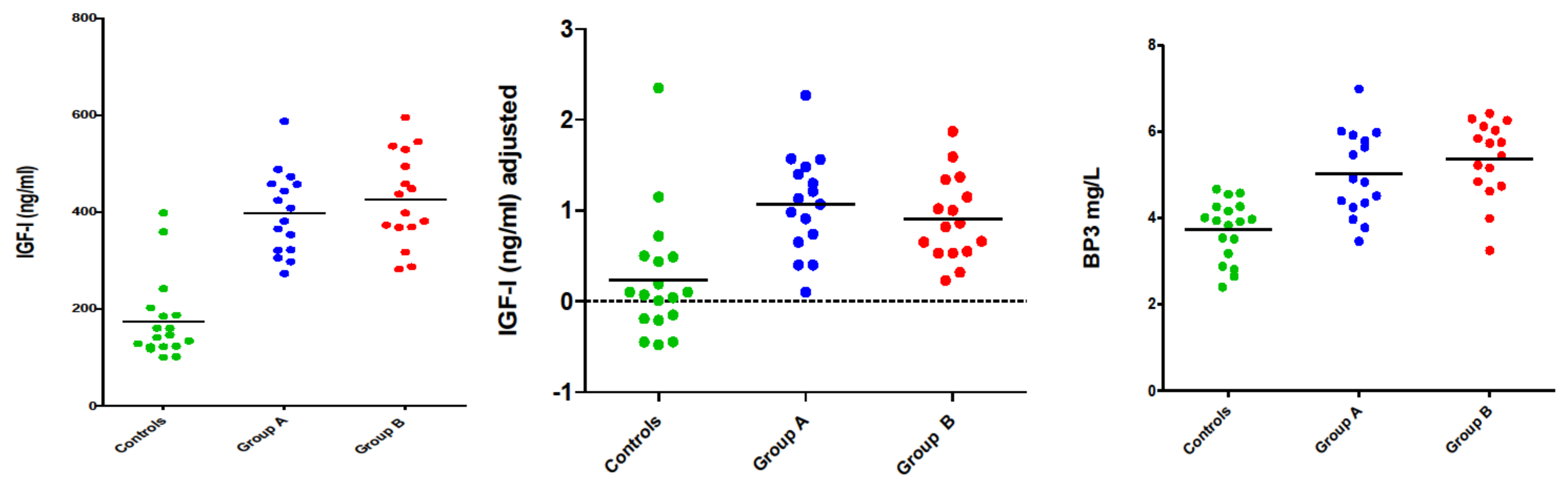

Figure 2: IGF-I (ng/ml) (adjusted for age and sex) and IGFBP-3 in controls, Group A and B. Bars represent medians.

No difference was found in IGF-I and IGFBP-3 levels between Group A and B, however, IGF-I and IGFBP-3 were higher in Group A and B than in Controls (p<0.0001).
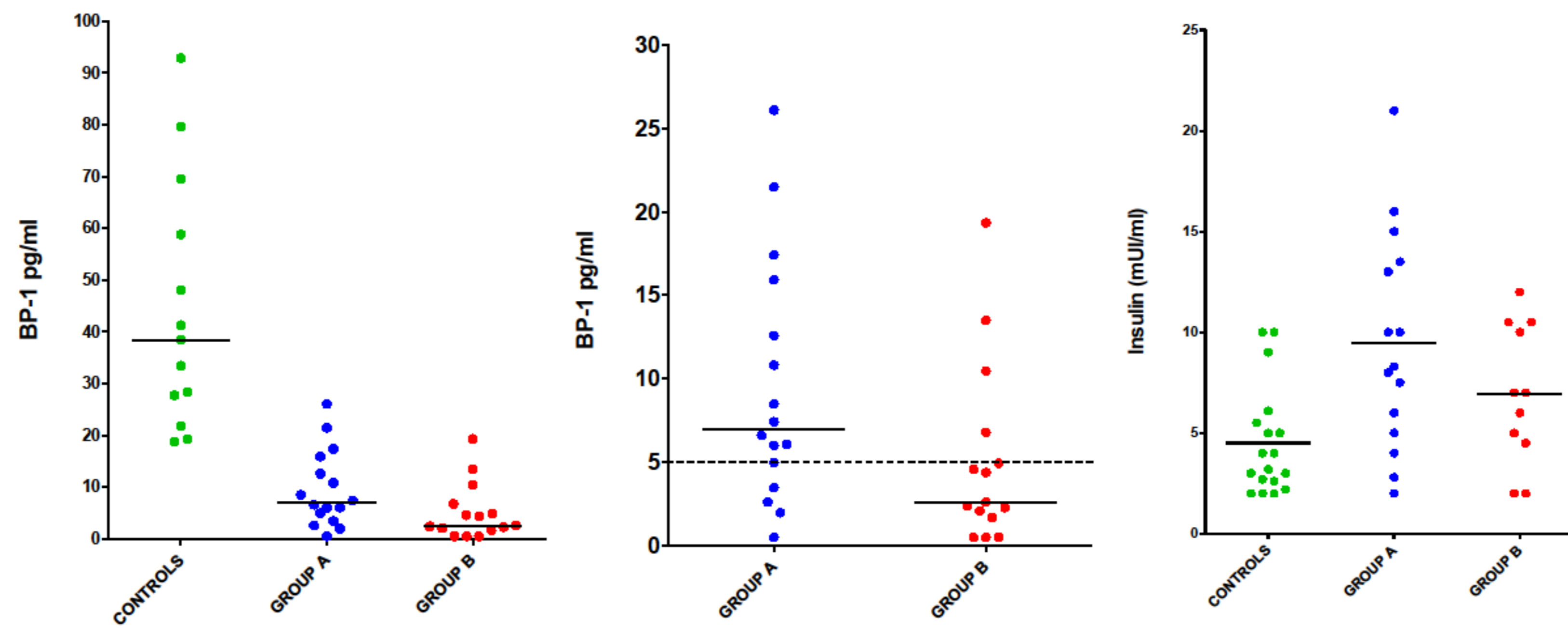

Figure 3: IGFBP-1 (ng/ml) and insulin (mUI/ml) in controls, Group A and Group B. Bars represent medians.

IGFBP-1 levels were higher in controls than in Group A and (p<0.0001).

IGBPB-1 < 5 ng/ml was more frequently observed in Group A than in Group B (p=0.01).

Insulin levels were lower in Controls than in Group A (p=0.01), but no difference were observed between Groups B and A.

Negative correlation was found between insulin and IGFBP-1 when controls and Group A were put together (r= -0.5; p=0.007). This correlation disappear if Group B is included in the analysis

Six girls were studied in two moments, before (A) and during GnRHa treatment (B). In this group IGF1R mRNA expression was also higher during GnRHa use (p<0.01) while IGF-I and IGFBP3 were similar in both evaluations.
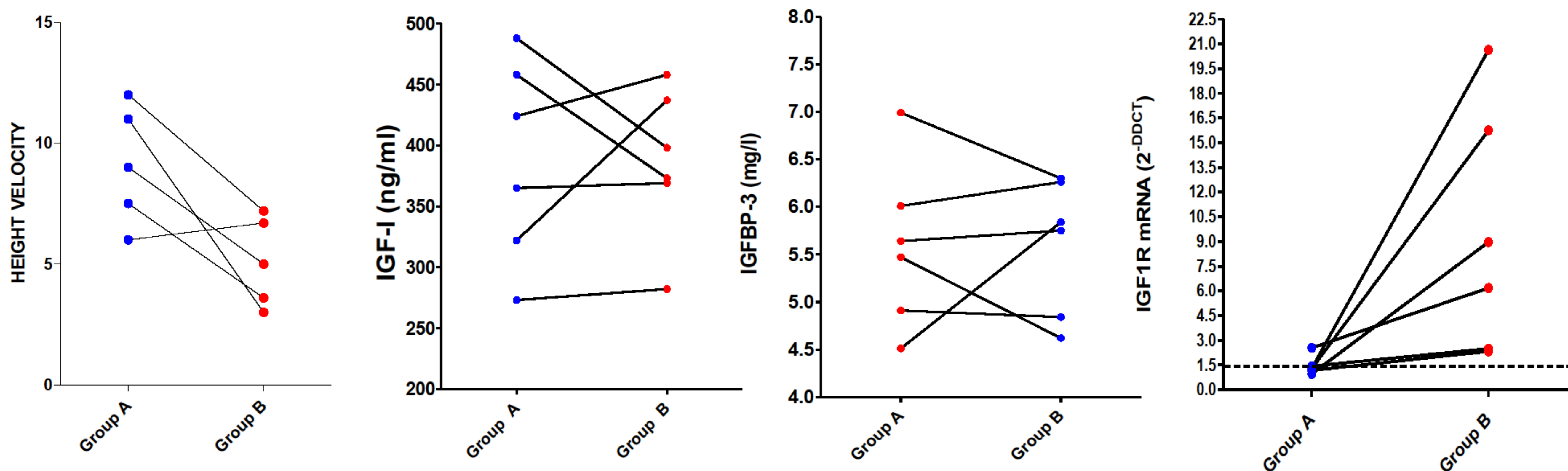

Figure 4: Height velocity, IGF-I, IGFBP-3 and IGF1R mRNA ($2^{-\Delta\Delta CT}$) expression of the 6 girls who were evaluated prospectively.

During GnRHa treatment:
- Height velocity decreased (p=0.04),
- IGF-I and IGFBP-3 did not change (p=1.0 and 0.8 respectively) and
- IGF1R mRNA ($2^{-\Delta\Delta CT}$) increased (p=0,008).

CONCLUSION: Decreasing in height velocity during CPP treatment with GnRHa can not be explained by changes in IGF-I availability. However, the increase in IGF1R mRNA expression suggest impairment of IGF-I signaling and compensatory up regulation of the IGF1R. Increased GH concentrations due to reduction of IGF-I feedback could explain the IGF-I, IGFBP-3 and IGFBP-1 findings.